Repeated measurements

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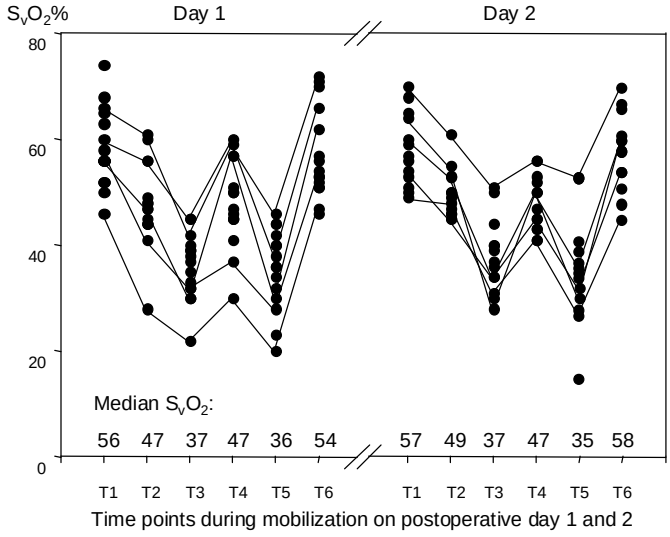
Repeated measurements

More or less equivalent to...

- Within subjects experiments
- Longitudinal data
- Grouped data
- (Time series)
- (Hierarchial models)

Repeated observations in the same individual:



Time points during mobilization on postoperative day 1 and 2

Repeated measurements

Advantages

- Every individual acts as his own control→ reduced intra-individual variation
- Effective use of recruited individuals

Problems

- Potential “carry-over” effect
- Spontaneous change over time
- Correlated observations in general: note that “usual statistical procedures” (e.g. testing the null hypothesis) requires independent observations!

Repeated measurements - overview

- What is the problem?
- Possible solutions:
  - Plot
  - Linear model with baseline value as covariate (Eivind Brønstad, MD)
  - One summary measure
  - Randomized blocks ANOVA
  - Friedman's test (a non-parametric alternative)
  - Repeated measurements ANOVA
  - Linear mixed effects model

Day I

Day II

Linear model with baseline value as covariate

Problem description

- To compare two independent groups (e.g. intervention/ control)
- Primary outcome: change from baseline. However, the outcome is likely related to the baseline.
- Irrespective of intervention, extreme baseline observations will tend towards the average at follow-up ("regression to the mean")
- Possible strategies:
  - Compare group outcomes without considering baseline (not very effective)
  - Compare change within each group (may be misleading)
  - Modeling the outcome in a linear model with baseline as covariate and group as factor. Recommended[1].
  - Equivalently, change from baseline may be modeled with baseline as covariate and group as indicator.

Vickers, A. J. and D. G. Altman (2001). Analysing controlled trials with baseline and follow up measurements." *BMJ* 323(7321): 1123-1124.

Another option:
one summary measure per individual

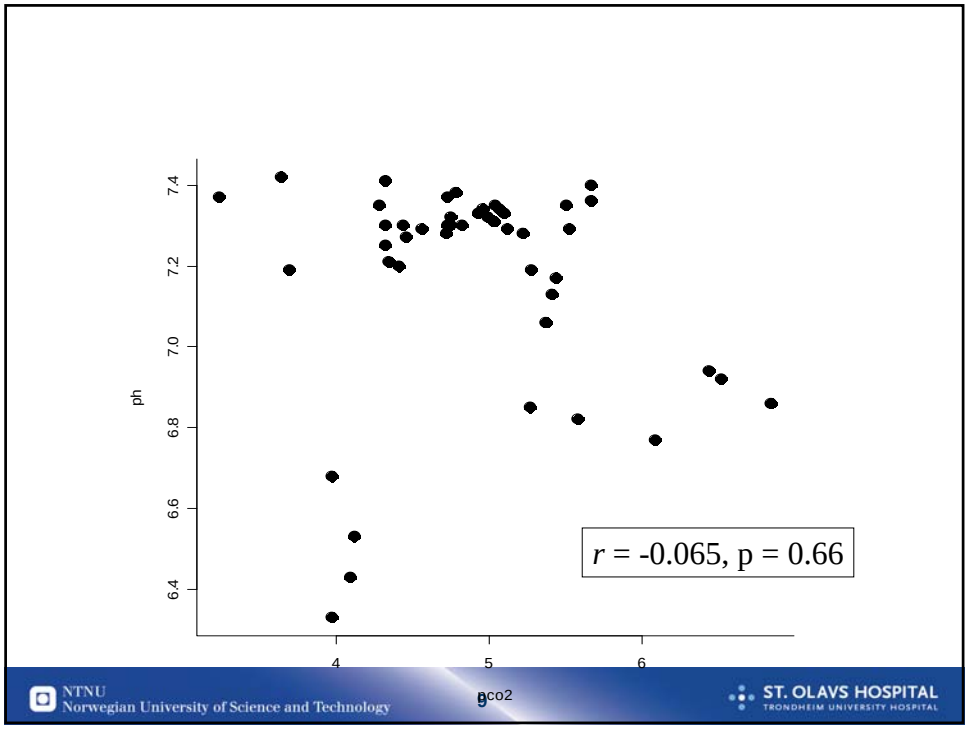
- Change
- Mean or median value
- Maximum value
- Maximum change
- Area under the curve (AUC)
- Estimated slope (β) for each individual obtained by simple linear regression

→ These outcomes may be analysed with “usual procedures” (t-tests etc.)
as observations are now independent

(Altman, 1991, Davis, 2002)

Example I: intramural pH vs. P_aCO_2

obs	id	ph	pco2
1	1	6.68	3.97
2	1	6.53	4.12
3	1	6.43	4.09
4	1	6.33	3.97
5	2	6.85	5.27
6	2	7.06	5.37
7	2	7.13	5.41
8	2	7.17	5.44
9	3	7.40	5.67
10	3	7.42	3.64
11	3	7.41	4.32
12	3	7.37	4.73
13	3	7.34	4.96
14	3	7.35	5.04
15	3	7.28	5.22
16	3	7.30	4.82
17	3	7.34	5.07
18	4	7.36	5.67
19	4	7.33	5.10
20	4	7.29	5.53
21	4	7.30	4.75
22	4	7.35	5.51
23	5	7.35	4.28
24	5	7.30	4.44
25	5	7.30	4.32
26	5	7.37	3.23
27	5	7.27	4.46
28	5	7.28	4.72
29	5	7.32	4.75
30	5	7.32	4.99
31	6	7.38	4.78
32	6	7.30	4.73
33	6	7.29	5.12
34	6	7.33	4.93
35	6	7.31	5.03
36	6	7.33	4.93
37	7	6.86	6.85
38	7	6.94	6.44
39	7	6.92	6.52
40	8	7.19	5.28
41	8	7.29	4.56
42	8	7.21	4.34
43	8	7.25	4.32
44	8	7.20	4.41
45	8	7.19	3.69
46	8	6.77	6.09
47	8	6.82	5.58


ph
7.4
7.2
7.0
6.8
6.6
6.4
4
5
6
pco2
r = -0.065, p = 0.66
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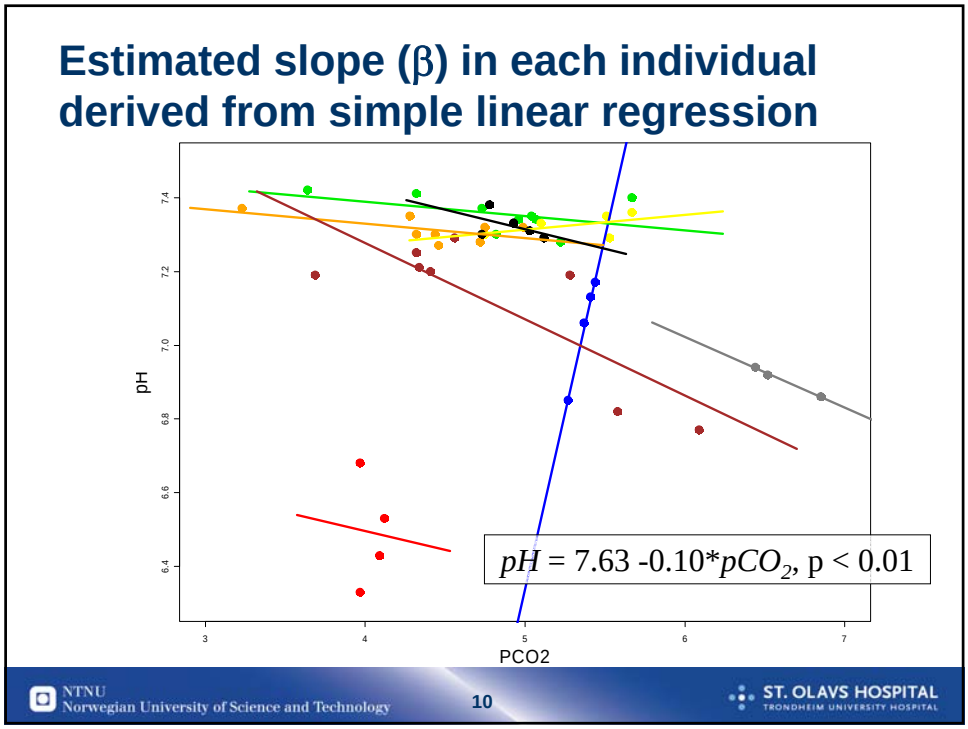
Estimated slope (β) in each individual derived from simple linear regression
pH
7.4
7.2
7.0
6.8
6.6
6.4
3
4
5
6
7
PCO2
pH = 7.63 -0.10*pCO2, p < 0.01
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Norwegian University of Science and Technology
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Example II: gastric tube to reduce postoperative nausea and vomiting (PONV)

- Double blind study at St. Elisabeth (dept. of cardiothoracic surgery)
- 30 / 29 patients without or with tube
- PONV registered (none / slight / some / much) every third hour, a total of 8-11 times per patient
- Does tube affect PONV?

Summary measure: maximum PONV
(i.e. did the patient report "much PONV" at <u>any</u> time?)

			Gastric tube		
			No	Yes	Total
PONV	None or slight	No.	18	24	42
		%	60,0%	82,8%	71,2%
	much	No.	12	5	17
		%	40,0%	17,2%	28,8%
Total		No.	30	29	59
		%	100,0%	100,0%	100,0%

Conditional test, exact p = 0.0848 (Fisher)
Unconditional test, exact p = 0.067

Example III: mobilization after cardiac surgery

- Observational study at St. Elisabeth
- Mixed venous oxygen saturation measured in the same patient at time points T1…T6:
  - At rest, in bed T1
  - Sitting in chair T2
  - Walking “on the spot” T3
  - Sitting in chair T4
  - Walking “on the spot” T5
  - At rest, in bed T6

Observations ...

Mobox_3_dag1.sav - SPSS Data Editor

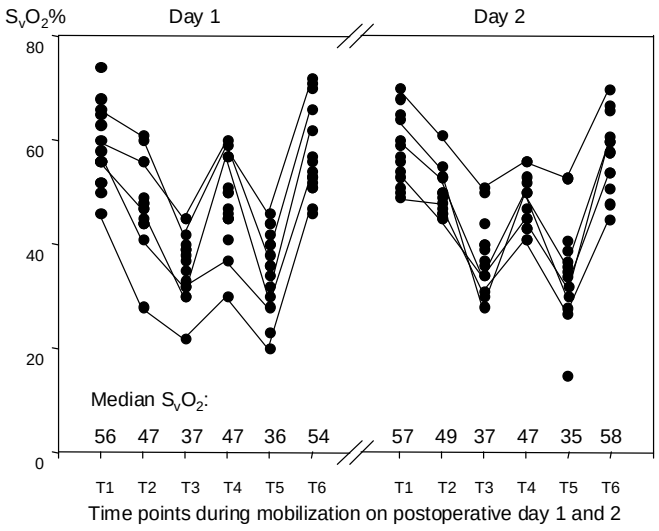
File Edit View Data Transform Analyze Graphs Utilities Window Help

One time point

One patient

	svo21.1	svo21.2	svo21.3	svo21.4	svo21.5	svo21.6	var
1	46	28	22	30	20	47	
2	56	47	30	57	30	62	
3	65	60	40	57	44	70	
4	52	44	35	45	34	52	
5	52	44	33	45	36	46	
6	66	61	42	59	46	71	
7	68	48	30	45	23	56	
8	56	48	38	47	40	54	
9	50	47	37	41	40	51	
10	60	56	45	60	38	66	
11	58	41	32	37	28	53	
12	56	45	39	50	36	51	
13	63	44	39	51	42	57	
14	74	56	45	50	44	72	
15	56	49	32	46	32	53	

Plot ...



Randomized blocks ANOVA

- The paired t-test extended to more than two groups
- Different treatments applied to the same individual (in random order - *not over time! This may yields autocorrelation*)
- Conceptual: 2-way ANOVA, without interaction
- Considers the individuals as “blocks”
- “Post-hoc” tests as usual

Friedman's test: a non-parametric analogue to randomized blocks ANOVA

- Block version of the Sign test / Kruskal-Wallis' test
- Different treatments applied to the same individual (in random order - *not over time! This may yield autocorrelation*)
- Conceptual: 2-way ANOVA without interaction, based on ranking the observations.
- Considers the individuals as "blocks"
- "Post-hoc" test:
  e.g. Wilcoxon's signed rank test, with Bonferroni correction acccording to design

Repeated measurements ANOVA - two approaches

Univariate (most intuitive)

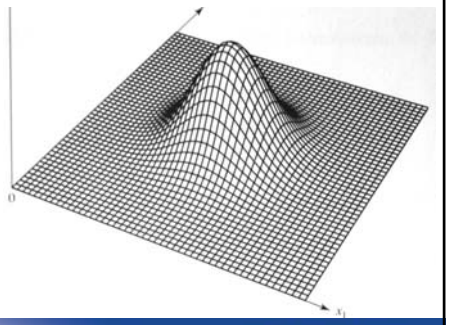
- One outcome variable;
  every "subject" (e.g. patient) is observed under different experimental conditions.
  - Within subjects factors
  - Between subjects factors
  - Covariates (continuous variables like age and weight)
- Largest power
- How to handle missing observations?
- Requires "sphericity": among other things equal correlation among all observations
  - Mauchly's test: checks the requirement of sphericity
  - The degrees of freedom of the global F-test may be adjusted accordingly. Stricter significance criteria. (Huyn-Feldt adjustment).

Repeated measurements ANOVA

Multivariate (less intuitive)

- Outcome variables are modelled simultaneously:
  Each ”subject” yields one observation on many outcome variables
  (as opposed to many observations of one outcome)
- Assumes multi-Normal distribution
- Very flexible correlation structure
- How to handle missing observations?
- More difficult interpretation
- Less power

multinormalfordeling, n = 2:



Repeated measurements ANOVA

- SPSS
  → General linear model → repeated measurements
- Kinnear & Gray chapter 9: “within subjects experiments”